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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/380,327	09/03/1999	SARAH ANNE ROBERTSON	A20-005	2475

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EXAMINER

BELYAVSKIY, MICHAEL A

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/380,327

Applicant(s)

ROBERTSON ET AL.

Examiner

Michail A. Belyavskiy

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 105-134 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 105-134 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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RESPONSE TO APPLICANT'S AMENDMENT

1. The **examiner** of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Michail Belyavskiy, Group Art Unit 1644, Technology Center 1600

2. Applicant's amendment, filed 01/05/05 is acknowledged.

Claims 105-134 are pending.

Claims 105-134 are under consideration in the instant application.

In view of the amendment, filed 01/05/05 the following rejections remain

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (9) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 105-112, 115-125, 127- 132 and 134 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 in view of Lea et al (Am J Reprod Immunol 34(1)), Nocera et al (Am J. Reprod. Immunology 33: 282-291, 1995); Clark et al (Hum Reprod 9(12): 2270-7, Dec 1994,), Thomas et al., (Am J Reprod. Immunol 644): 185-9, Dec 1984;), Thaler et al (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989;) and Prakash et al., 1 (Reproductive Immunology 70: 403-412, 1981) in view of the known fact disclosed in the Specification on

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overlapping pages 10-11, for the same reasons set forth in the previous Office Action, mailed on 10/06/04

Applicant's arguments, filed 01/05/05 have been fully considered, but have not been found convincing.

Applicant asserts that: (i) US Patent '825 does not suggest a method of treating recurrent miscarriage by inducing specific immune tolerance to a paternal antigen in a mammalian prospective mother lacking said immune tolerance; (ii) none of the secondary references teach or suggest a method of treating infertility by the induction of immune tolerance by exposing a mucosal surface of the prospective mother to semen or MHC class I antigen; (iii) the state of the prior art teach away from the invention, as evidenced by the attached references of the Exhibit A-C.

Applicants have traversed the primary and the secondary references pointing to the differences between the claims and the disclosure in each reference. Applicant is respectfully reminded that the rejection is under 35 USC103 and that unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see *In re Keller*, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. *In re Young* 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

As was stated in the previous Office Action, US Patent '825 teaches a method of treating infertility by administering TGF β , such as TGF β 1, TGF β 2, TGF β 3, and TGF β 4 (See column 5, line 9-11, in particular) along with antigens such as sperm into the reproductive tract (genital mucosal surface) of the a female to bolster the chances that a pregnancy will be sustained by increasing the success rate of implantation (See column 5 line 9-12, claim 4 of US Patent' 825 patent, in particular). The reference TGF β may be administered either before, after or simultaneously with the male antigens such sperms of the prospective father which are known to express MHC class I molecule on the surface (sperm antigens) and antigens from the conceptus to the mucosal surface wherein the mucosal surface is the reproductive tract of a female (See claims 1-5, column 6 line 67 bridging column 7 line 23; column 4, line 12-21, in particular). The reference TGF β may be administered by intravenous injection (systemic contact), patch, and gels that are slow release (See column 5, line 1-2, column 6, line 45-55, in particular). The US Patent' 825 further teaches a method of diagnosing or testing the presence of active and/or immunological TGF β in female or diagnosing mammals with infertility due to inadequate TGF β (See column 6, line 8-16, column 3, lines 59-65, in particular). The reference method also can be used in conjunction with assisted reproduction such as IVF (See column 3 lines 66 bridging column 4, lines 6, in particular). The US Patent' 825 teaches that TGF β stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document, Claims of 825 patent, in particular).

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The claimed invention in claim 105 differs from the teachings of the reference only in that the method of treating recurrent miscarriage by inducing immune tolerance by exposing mucosal surface of prospective mother with semen or MHC class I antigen of a prospective father capable of eliciting a Th-1 response and substantially purified TGF β .

The Specification on overlapping pages 10-11 disclosed that it was well known to one ordinary skill in the art at the time the invention was made that recurrent miscarriage is infertility disease and couple with said problem should be treated together.

Lea et al., teach infertile patients with recurrent spontaneous abortion is deficient in TGF β producing suppressor cells in uterine tissue near the placental attachment site (See abstract, in particular).

Nocera et al., teach human seminal plasma contains both TGF β such as TGF β 1 and TGF β 2 and is biologically activated from high molecular weight latent TGF β by acid pH environment of female lower genital tract. Activation of seminal plasma TGF β may immunologically protect the integrity of sperm (See abstract, in particular) and a reduced level of the seminal plasma TGF β may potentially render the spermatozoa immunogenic and lead to the attack by the lymphocytes and other immune cells of the female host (See page 290 paragraph bridging col. 1 and 2, in particular). Nocera et al., further teach TGF-j has been shown to inhibit the generation and killing activity of m-2 activated NK cell (LAK) (See page 283, col. 1, par. 2, in particular).

Clark et al., teach that bioactive TGFS is known to suppress the generation of cytotoxic cells in vitro and has immunosuppressive activity in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Thomas et al teach seminal plasma abrogates the postcoital T cell response to spermatozoal histocompatibility antigens (See abstract, in particular).

Thaler et al., teach seminal plasma regulates maternal immunity for insemination and pregnancy. Seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle (See abstract, in particular).

Prakash et al., teach exposing genital mucosal surface of prospective mother to semen through coitus in the form of ejaculate is a form of immunization. During coitus, the female receives in her reproductive tract (mucosal surface) semen from a genetically dissimilar male. The semen contains immunogenic autoantigens, alloantigens, sperm proteins and seminal plasma adsorbed on sperm surface which are highly immunogenic. However, the female reproductive tract does not appear to be an immunologically privileged site. A potent inhibitor of immune response was indeed found in semen (See page 405, in particular).

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to treat recurrent miscarriage, by inducing immune tolerance to a paternal antigen by exposing the female genital mucosal surface of the prospective mother to semen in the form of ejaculate of the prospective father as taught by Prakash et al, Thaler et al and Thomas et al, because recurrent miscarriage is an infertility disease as taught by the known fact disclosed in the Specification on overlapping pages 10-11, along with immunosuppressive factor derived from seminal plasma such as TGF β 1 or TGF β 2 that suppresses postcoital T cell response as taught by Thomas, prime mothers prior to fertilization for pregnancy acceptance which is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle as taught by Thaler et al, and increasing the success rate of implantation for treatment of infertility such as early embryonic loss, implantation failure, spontaneous abortion and preeclampsia associated with IVF as taught by the US Patent '825.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Lea et al teach infertile patients with recurrent spontaneous abortion is deficient in TGF β 2 producing suppressor cells in uterine tissue near the placental attachment site (See abstract, in particular). The US Patent '825 teaches that TGF β stimulates the production of trophoblast fibronectin for increasing the success rate of implantation (See entire document).

Clark et al., teach bioactive TGF β is known to suppress the generation of cytotoxic T cells in vitro and has immunosuppressive activity that leads to induction of tolerance in vivo during the first trimester pregnancy in humans (See abstract, in particular).

Nocera et al., teach human seminal plasma contains both TGF β such as TGF β 1 and TGF β 2 and TGF β 1 and TGF β 2 are biologically activated from high molecular weight latent TGF β by acid pH environment of female lower genital tract. Thaler et al teach seminal plasma contains factors that specifically suppressive the effects on female alloimmune response to paternally derived alloantigens and could prime mothers prior to fertilization for pregnancy acceptance and is supported by improved implantation rates in controlled clinical trials using timed vaginal exposure to semen during in vitro fertilization or gamete intrafallopian transfer treatment cycle (See abstract, in particular).

Claims 107-111 are included in this rejection because the recitation of administering systemically TGF β and one or more antigens or TGF β and one or more antigens each administered at a first site and a different site is an obvious variation of the teaching of US Patent '825 because US Patent '4825 teaches that TGF β can be administered simultaneously, before or after the antigen and the sites of administration is within the purview of one ordinary skilled in that art at the time the invention was made.

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Claim 124 is included because it is an obvious variation of the TGF β since Nocera et al teach human transforming growth factor- β (TGF β) such as TGF β 1 and TGF β 2 are biologically activated from high molecular weight latent TGF β by acid pH environment of female lower genital tract or plasmin. The recitation of active form is within the teachings of

US Patent '825 because administering TGF β and antigens lead to increase the success rate of implantation, which is the active form of TGF β (See entire document, Claims of 825 patent, in particular).

Claims 127-131 are included because the recitation of multiple exposure and dosing schedule to TGF β and semen or MHC class 1 antigen of the prospective father prior to attempted conception is within the purview of one of ordinary skilled in the art based on the teachings of the Us Patent '825.

Claims 115 and 120-123 are included because it is well within the purview of one of ordinary skill in the medicinal art to optimize doses for the particular treatment regimen. In re Aller, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP j 2144.05 part 11 A.

5. Claims 113 and 114 stand rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 in view of Lea et al (Am J Reprod Immunol (34(1)), Nocera et al (Am J. Reprod. Immunology 33: 282-291, 1995) ; Clark et al (Hum Reprod 9(12): 2270-7, Dec 1994,), Thomas et al., (Am J Reprod. Immunol 644): 185-9, Dec 1984;), Thaler et al (Am J Reprod Immunol 21(3-4): 147-50, Nov-Dec 1989;) and Prakash et al., (Reproductive Immunology 70: 403-412, 1981;) in view of the known fact disclosed in the Specification on overlapping pages 10-11 as applied to claims 105-112, 115-125, 127- 132 and 134 above and further in view of Harlow et al., (of record, in A Laboratory Manual, Cold Spring Harbor Laboratory, page 61, 1988'), World Health Organization (of record, in World Health Organization Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction, Cambridge University Press, (NY 1987) and Martin-Villa et al (, Biol Reprod 5543): 620-9, Sept 1996,) for the same reasons set forth in the previous Office Action, mailed on 10/06/04

Applicant's arguments, filed 01/05/05 have been fully considered, but have not been found convincing.

Applicant asserts that claims 113 and 114 depends from independent claim 105 which is nonobvious.

As has been discussed supra, it is the Examiner position that independent claim 105 is obvious in view of combined teachings of US Patent '825, Lea et al, Nocera et al, Clark et al, Thaler et al, Thomas et al., and Prakash et al and the known fact disclosed in the Specification on overlapping pages 10-11.

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The claimed invention as recited in claim 113 differs from the combined teachings only in that the instant claim recited that the semen or MHC Class I antigen is presented in purified form instead of semi-purified form.

The claimed invention as recited in claim 114 differs from the combined teachings only in that the instant claim recited that purified semen or MHC Class I antigen is present on an inert or adjuvant carrier.

Harlow et al teach a simple method of purifying any protein antigen by polyacrylamide gels electrophoresis (See page 61, in particular). Harlow et al., teaches that having pure antigen provides the best case for the production of antibodies.

The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining and purifying sperm of a prospective father's ejaculate (See page 5, page 9, Counting the spermatozoa, in particular) and various methods of determining male infertility.

Martin-Villa et al teach a method of purifying sperm in semen and determining antigen density such as HLA on cell surface using double labeling cytofluorometry and relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA (See entire document, Abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to purify MHC class I antigen as taught by Harlow et al, the WHO laboratory manual and Martin-villa et al using the antigens from the sperm or conceptus as taught by the US Patent'825 for a method of treating recurrent miscarriage by induction of tolerance to paternal antigen as taught by the US Patent' 825, Lca et al, Nocera et al, Clark et al, Thaler et al., Thomas et al., and Prakash et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Harlow et al teach purifying any protein antigen by polyacrylamide gels electrophoresis is a simple method (See page 61, in particular). The WHO Laboratory Manual for the Examination of Human Semen and Semen Cervical Mucus Interaction teaches a method of determining sperm count of a prospective father's ejaculate is useful for (See page 5, page 9, Counting the spermatozoa, in particular) determining male infertility. Martin-villa et al teach a method of purifying sperm in semen and determining antigen density such as HLA on cell surface using double labeling cytofluorometry using relevant antibody and HLA-bearing spermatozoa are more capacitated for fertilization than those do not bear HLA as one of the indicator for male fertility (See entire document, Abstract, in particular).

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6. Claim 126 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDSI in view of Lea et al (Am J Reprod Immunol 3441): 52-64, July 1995; PTO 892), Nocera et al (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark et al (of record, Hum Reprod 9412): 2270-7, Dec 1994, PTO 892), Thomas et al (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler et al., (Am J Reprod Immunol 2143-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash et al., (Reproductive Immunology 70: 403-412, 1981; PTO 892) in view of the known fact disclosed in the Specification on overlapping pages 10-11 as applied to claims 105-112, 115-125, 127- 132 and 134 above and further in view of Grainger et al (Nat Med 149): 932-7, Sep 1995; PTO 892) for the same reasons set forth in the previous Office Action, mailed on 10/06/04

Applicant's arguments, filed 01/05/05 have been fully considered, but have not been found convincing.

Applicant asserts that claim 126 depends from independent claim 105 which is nonobvious.

As has been discussed supra, it is the Examiner position that independent claim 105 is obvious in view of combined teaching of US Patent '825, Lea et al, Nocera et al, Clark et al, Thaler et al, Thomas et al., and Prakash et al and the known fact disclosed in the Specification on overlapping pages 10-11.

The claimed invention as recited in claim 126 differs from the combined teachings of the references only in that the method of treating recurrent miscarriage includes administration of plasmin as to increase the level of active TGF β .

Grainger et al teach transforming growth factor beta 1 (TGF-beta 1) is a platelet-derived cytokine and human whole platelets is a rich source of inactive TGF-beta 1, which can be activate by plasmin (See abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the active TGF β as taught by the US Patent '825 for the unpurified form using a biological source rich in TGF β such as the platelets along with plasmin to activate the inactive form of TGF β as taught by Grainger et al for a method of eliciting an immune reaction in a prospective mammalian mother comprising exposing said prospective mother to one or more antigens of said prospective father and substantially purified TGF β said mother leading to tolerance to one or more antigens and alleviation of symptoms of infertility condition as taught by the US Patent '825, Lea et al, Nocera et al, Clark et al, Thaler et al, Thomas et al., and Prakash et al and the known fact disclosed in the Specification on overlapping pages 10-11. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

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One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Grainger et al teach platelet is a rich of inactive TGF β and which can be activated by plasmin.

7. Claim 133 stands rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 5,395,825 (of record, May 1995; IDS in view of Lea et al (Am J Reprod Immunol 3441): 52-64, July 1995; PTO 892), Nocera et al (Am J. Reprod. Immunology 33: 282-291, 1995; PTO 892), Clark et al (of record, Hum Reprod 9412): 2270-7, Dec 1994, PTO 892), Thomas et al (Am J Reprod. Immunol 6(4): 185-9, Dec 1984; PTO 892), Thaler et al., (Am J Reprod Immunol 2143-4): 147-50, Nov-Dec 1989; PTO 892) and Prakash et al., (Reproductive Immunology 70: 403-412, 1981; PTO 892) in view of the known fact disclosed in the Specification on overlapping pages 10-11 as applied to claims 105-112, 115-125, 127- 132 and 134 above and further in view of Heidenreich et al., (Am J Reprod Immunol 1994, 3142-3: 69-76,) for the same reasons set forth in the previous Office Action, mailed on 10/06/04

Applicant's arguments, filed 01/05/05 have been fully considered, but have not been found convincing.

Applicant asserts that claim 133 depends from independent claim 105 which is nonobvious.

As has been discussed supra, it is the Examiner position that independent claim 105 is obvious in view of combined teaching of US Patent '825, Lea et al, Nocera et al, Clark et al, Thaler et al, Thomas et al., and Prakash et al and the known fact disclosed in the Specification on overlapping pages 10-11.

The claimed invention as recited in claim 133 differs from the teaching of the combined references only in that the method of treating recurrent miscarriage includes testing whether anti-sperm antibodies exist.

Heidenreich et al teach a method of detecting anti-sperm antibody in infertile male using a highly sensitive and reproducible ELISA assay (See abstract, in particular). The reference assay synchron ELISA (Synelisa) is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the step of diagnosing whether anti-sperm antibodies exist using the assay as taught by Heidenreich et al with the method of treating recurrent miscarriage by administering TGF β and male antigen as taught by combined teaching of US Patent '825, Lea et al, Nocera et al, Clark et al, Thaler et al, Thomas et al., and Prakash et al and the known fact disclosed in the Specification on overlapping pages 10-11.

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From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention. One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Heidenreich et al teach anti-sperm antibody is associated with male infertility and the reference assay is useful for is highly sensitive and reproducible since the assay does not require fixation of the sperm surface antigens by formaldehyde or glutaraldehyde and the structure of sperm surface antigens is not altered by the fixation process.

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskiy whose telephone number is 571/ 272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michail Belyavskiy, Ph.D.
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Technology Center 1600
March 21, 2005


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